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POWDER PREPARATION FOR INHALATION5 Technical field

10 This invention relates to a method for the administration of a peptide or a protein to the airways and a pharmaceutical powder formulation for inhalation containing a peptide or a protein. The protein is preferably insulin.

Background of the invention

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The normal insulin secretion is disturbed or non existing in patients suffering from diabetes mellitus. The disease is treated by parenteral injections of insulin. Since insulin is a protein hormone, it is susceptible to proteolytic degradation in the gastrointestinal tract and is therefore not suitable for oral administration. The ordinary route of administration is subcutaneous or intramuscular injection. These modes of administration have two apparent disadvantages:

25 1) Repeated, sometimes life-long use of injections, are inconvenient, unpractical and often painful for the patients.

30 2) The plasma concentration curve of insulin in healthy humans is governed by the intake of food, which results in a high plasma insulin concentration in connection with meals and a low concentration between the meals. As the absorption rate from the subcutaneous/intramuscular site is slow, the plasma concentration curve of insulin after injection is flat and drawn out, often giving too high insulin levels between meals. This abnormal plasma concentration profile might increase the risk of side effects related to long term treatment of diabetes.

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Many attempts have been made to overcome these problems, for example by administration by other routes, as nasal, buccal and rectal delivery, but without resulting in successful products. Much work has been devoted to nasal administration, including clinical trials, but the attempts have not been successful so far. The epithelial membrane in the nasal cavity has low permeability for insulin, which, leads to a very low bioavailability. The absorption rate can be promoted by incorporation of enhancers of different types, but as they have to be included in relatively high concentrations, the risk of local irritation and damage of the epithelial cells is obvious. Temporary fluctuations of the conditions in the nose, e. g. caused by infections and environmental conditions, decreases the predictability of the absorption rate. In the nasal cavity, the proteins are also exposed to proteolytic enzymes.

Today many drugs are delivered to the lungs for local treatment, but pulmonary delivery of systemically active drugs, including insulin, have gained increasing interest. Some studies of insulin delivery to the lungs have also been published. In these investigations, water solutions of insulin have been delivered as droplets to the lungs in humans by a nebulizer (Laube et al., Köhler). The results from these studies indicate, that insulin is absorbed, but to a variable and limited extent. The use of nebulizers is also unpractical and technically complicated.

The use of metered dose inhalers, driven by propellants, for insulin delivery is conceivable, but the use of propellants is not unobjectionable. Even if the problem with ozone depletion is solved, problems with local irritation of propellants and lubricants in the airways may still remain. Many patients also have difficulties to

use the inhaler correctly.

There is a need for an improved system for delivery of insulin in a manner which gives fast and substantial  
5 absorption.

Outline of the invention

10 The present invention provides delivery of insulin by inspiratory flow driven powder inhalers. These types of inhalers contain no propellant or lubricant. They are breath-operated and require no coordination between actuation and inhalation and are therefore easy to use. Delivery of an insulin powder formulation by this type of  
15 devices provides fast and substantial absorption and is a real progress in the treatment of diabetes mellitus.

When administering powder preparations, containing insulin and lactose, to dogs and rats by inhalation it is  
20 found that, although insulin was absorbed from these preparations, the rate and amount of absorption was too low to be considered therapeutically sufficient.

On the other hand, we have found that when certain  
25 surfactants are included in the preparation, the rate and amount of absorption are considerably increased. It has also been found that by this mode of administration insulin mimics the pharmacokinetic profile of insulin in healthy persons. This has led us to the conclusion, that  
30 this could be a way of insulin administration for diabetics, which would simulate the normal physiological behaviour of insulin in vivo.

The absorption enhancing effects are also present for  
35 other peptides and proteins.  
An object of the present invention is to provide a method for the administration of a peptide or a protein,

particularly insulin to the airways of a patient characterized by administering a dry powder for inhalation of a peptide or a protein and a substance which enhances the absorption of the peptide or the protein in the lung.

A further object of the invention is to provide a pharmaceutical composition for inhalation characterized in that it comprises a dry powder mixture of a peptide or a protein, particularly insulin and a compound which enhances the absorption of the peptide or the protein in the lung.

The reference below is to insulin, but is equally valid for other peptides or proteins.

The main component of the powder is insulin, with a low particle size. We have used human insulin, but other types of insulin as well as analogues are of course possible. The particles should have a mass median diameter between 1-10  $\mu\text{m}$ , and preferably between 1 and 5  $\mu\text{m}$ , in order to achieve acceptable deposition in the lungs. The insulin quality should have low content of Zn and be in a solid state which gives fast dissolution and high solubility in aqueous solutions.

Beside insulin, the powder should comprise a component which enhances the absorption of insulin through the epithelial layers in the lungs. This component should also be micronized by the same reasons as insulin. This component should have the following properties:

- 1) Good powder properties, i.e. have no tendency of stickiness
- 2) Stable in solid state
- 3) Should not affect the insulin stability
- 4) Low local and systemic toxicity

- 5) Good promotion of insulin absorption
- 6) Not hygroscopic

We have found that salts of fatty acids, with preferably 8-12 carbon atoms, possess the desired properties. The counterion is preferably Na or K, but other inorganic or organic counterions are possible.

As examples could sodium, potassium, lysine, and arginine salts of caprylic, capric, and lauric acids or mixtures of these be mentioned.

The preferred enhancer is sodium caprate (sodium decanoate;  $\text{CH}_3(\text{CH}_2)_8\text{COONa}$ ).

No further ingredients are needed for the action of the preparation, but may be included for special reasons. In order to adjust the powder amount needed for one dose, the powder could be diluted by inactive compounds, such as lactose and mannitol.

Besides insulin other peptides and proteins could be used according to the invention. Such peptides and proteins could be calcitonin, anterior pituitary hormones (e.g. human growth hormone, adreno corticotropin) or posterior pituitary hormones (e.g. vasopressin).

The described powder preparation could be manufactured in several ways by conventional techniques.

The easiest way is to dry mix insulin and enhancer and then micronize the substances together. It is also possible to micronize the substances one by one and then mix them with a special technique. If needed the micronized powder could be processed to improve the flow properties, e.g. by dry granulation, before it is filled in the intended device.

It is also possible to dissolve or disperse the components in a suitable solvent, e.g. water, to obtain a homogeneous mixture. This procedure also makes it possible to adjust the pH-value to a desired level. It is known that the absorption of insulin is affected by the pH-value of the preparation, with increasing absorption when moving from the isoelectric point of insulin, which is around 5,5. However, the stability of the preparation and the pharmaceutically accepted limits of 3,0 and 8,5 for inhalation products must be taken into account. To obtain a powder, the components must be separated from the liquid by a suitable process with no or only little deterioration of the activity of the insulin. Among possible methods precipitation vacuum concentration, open drying, spray drying, and freeze drying could be mentioned, sometimes followed by grinding. If necessary, the dry powder is micronized. When a dry powder is obtained, the same steps as described above could be used to obtain the filled inhalation device.

The proportions of insulin and enhancer is mainly determined of what balance between desired and undesired effects is accepted. The proportion of the enhancer must attain a certain level for a sufficient improvement of the insulin absorption. On the other hand, the content of enhancer should be kept low to minimize the risk of unwanted effects of the enhancer. For sodium caprate it has been found that acceptable absorption is achieved if the sodium caprate amount is not less than 5% preferably 10% and most preferably 25% of the insulin amount.

#### Working examples

Several formulations have been manufactured and tested in animal models, and the results have been very convincing. The following description acts only as an example of how

an efficient formulation can be prepared.

9.75 g of human insulin and 250 ml water is added to a beaker. The pH is lowered to 3.4 with 1 M HCl and then  
5 raised to 7.4 with 1 M NaOH in order to dissolve the insulin. 3.25 g sodium caprate is added and the pH is again adjusted to 7.4. The solution is stirred, and when the solution is clear or weakly opalescent, it is concentrated by evaporation at 37°C in about 2 days. The  
10 obtained solid cake is crushed and then sieved through a 0.5 mm sieve. The powder is micronized in a jet mill to particles with a mass median diameter of about 2  $\mu$ m. This micronized powder, containing 75 % insulin and 25 % sodium caprate is then filled into special inhalation  
15 apparatus and delivered to animals. Blood glucose and plasma insulin values are measured with certain time intervals.



The results from an inhalation study in two dogs are summarized in the tables below.

The given dose to dog 1 and dog 2 was 2.1 and 2.9 Iu/kg body weight respectively.

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#### Blood sampling dog 1

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Blood sample time after end of expo (minutes)	Blood glucose (mmol/L)	Insulin conc ( $\mu$ U/ml)
before	3.9	6.70
0.5	3.6	120.66
5	2.8	194.47
10	2.6	195.39
20	n.d.	139.74
22.5	1.6	n.d.
31	2.0	73.42
45	1.7	47.49
59.5	1.7	36.21
89.5	2.3	19.28
120	3.0	14.58
240	4.5	5.28

n.d. = not determined

## Blood sampling dog 2

5	Blood sample time after end of expo (minutes)	Blood glucose (mmol/L)	Insulin conc ( $\mu$ U/ml)
	before	3.9	44.84
	3	4.2	165.10
	6	4.3	158.28
10	12	3.9	n.d.
	14	n.d.	180.72
	19	3.0	133.75
	30	2.7	143.71
	45	2.5	91.62
15	60	2.4	66.70
	90	2.7	38.58
	122	3.7	29.15
	241	4.1	n.d.
	242.5	n.d.	19.76
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n.d. = not determined

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It is obvious from the tables that the formulation markedly increases the plasma level of insulin and decreases the blood glucose. The peak insulin values are

reached after 5-15 minutes and the corresponding decrease in blood glucose after 25-60 minutes. The plasma profile mimics the normal physiological plasma profile, in contrast to subcutaneous administration.

## CLAIMS

1. A method for the administration of a peptide or a protein to the airways of a patient characterized by  
5 administering a dry powder for inhalation of the peptide or the protein and a substance which enhances the absorption of the peptide or the protein in the lung.
2. A method according to claim 1 characterized in that  
10 the protein is insulin.
3. A method according to claims 1 or 2 characterized in that the compound which enhances the absorption of the peptide or the protein in the lung is a salt of a fatty  
15 acid.
4. A method according to claims 1-3 characterized in that the compound which enhances the absorption of the peptide or the protein in the lung is sodium caprate.  
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5. A pharmaceutical composition for inhalation characterized in that it comprises a dry powder mixture of a peptide or a protein and a compound which enhances the absorption of the peptide or the protein in the lung.  
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6. A pharmaceutical composition according to claim 5 characterized in that the protein is insulin.
7. A pharmaceutical composition according to claims 5 or  
30 6 characterized in that the compound which enhances the absorption of the peptide or the protein in the lung is a salt of a fatty acid.
8. A pharmaceutical composition according to claims 5-7  
35 characterized in that the compound which enhances the absorption of the peptide or the protein in the lung is sodium caprate.

9. A pharmaceutical composition according to claims 5-8 characterized in that the composition is dispensed in a powder inhaler.

5 10. A method for the treatment of diabetes mellitus comprising administering to a patient suffering therefrom in powder form an amount of insulin and a substance which enhances the absorption of insulin in the lung, sufficient for the treatment of said disease.

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11. Use of a peptide or a protein and a substance which enhances the absorption of the peptide or the protein in the lung in the form of a powder for inhalation.

15 12. Use according to claim 11 wherein the protein is insulin.

13. Use according to claims 11 or 12 wherein the substance which enhances the absorption of the peptide or  
20 the protein in the lung is a salt of a fatty acid.

14. Use according to claims 11-12 wherein the substance which enhances the absorption of the peptide or the protein in the lung is sodium caprate.

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15. A pharmaceutical composition for the use in diabetes treatment, wherein insulin and a substance which enhances the absorption of insulin in the lung is administered in the form of a dry powder for inhalation.

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16. A pharmaceutical composition according to claim 15 wherein the substance which enhances the absorption of insulin in the lung is a salt of a fatty acid.

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17. A pharmaceutical composition according to claims 15-16 wherein the substance which enhances the absorption of insulin in the lung is sodium caprate.

18. A process for the preparation of a pharmaceutical composition according to claim 5 characterized by either

5 a) dry mixing a peptide or a protein and a substance which enhances the absorption of the peptide or the protein in the lung and thereafter micronizing the obtained mixture, or

b) micronizing the components separately and thereafter mixing them, or

10 c) dissolving or dispersing the components in a suitable solvent and thereafter removing the solvent in order to obtain a dry powder and if necessary, micronizing the dry powder.

19. Use of a composition according to claims 6-9 in the

15 preparation of an active dosage form for the treatment of diabetes.

20. A powder inhaler containing a pharmaceutical composition according to any of claims 5-8 and 15-17.

# ABSTRACT

5 A method for the administration of insulin or another  
peptide or protein and a substance which enhances the  
absorption of the peptide or protein in the lung in the  
form of a dry powder for inhalation and a pharmaceutical  
powder formulation containing insulin or another peptide  
or protein and a substance which enhances the absorption  
of the peptide or protein in the lung.

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